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EXAMINER

LAMBERTSON, DAVID A

ART UNIT PAPER NUMBER

1636

DATE MAILED: 08/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/847,355

Applicant(s)

MORRIS ET AL.

Examiner

David Lambertson

Art Unit

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-25 is/are pending in the application.
- 4a) Of the above claim(s) 25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-24 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 & 6.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I is acknowledged.

Claim 25 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group, there being no allowable generic or linking claim. Election was made **without** traverse.

Claims 1-24 are pending in the application.

Priority

Applicant's claim for domestic priority concerning provisional applications 60/201,990, 60/205,389, 60/268,054, and 60/276,782 under 35 U.S.C. 119(e) is acknowledged. However, the provisional application 60/201,990 upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 2-8 and 10-23 of this application. In summary, provisional application 60/201,990 only discloses information concerning reoviruses and their effects on ras-activated neoplastic cells in cellular compositions, and does not adequately describe any of the elements recited in the aforementioned claims. Additionally, the provisional application 60/205,389 upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 5-8 and 10-20 of this application. In summary, provisional application 60/205,389 only discloses information concerning reoviruses and their effects on ras-activated neoplastic cells in cellular compositions, which include hematopoietic cells isolated from bone marrow or the blood of individuals, and the subsequent storage of the resulting cells in DMSO,

Art Unit: 1636

and does not adequately describe any of the elements recited in the aforementioned claims. Furthermore, the provisional application 60/268,054 upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 10-20 of this application. In summary, provisional application 60/268,054 only discloses information concerning reoviruses and their effects on ras-activated-neoplastic cells in cellular compositions, which include semen or donor eggs, hematopoietic cells isolated from bone marrow or the blood of individuals and tissues or organs, and the subsequent storage of the resulting cells in DMSO, and does not adequately describe any of the elements recited in the aforementioned claims. Priority to the individual claims will be assessed as set forth above.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for selectively removing neoplastic cells with hyperactive ras pathways, defective p53 alleles (or a deletion of p53), and suppressed immune responsiveness, does not reasonably provide enablement for selectively removing any neoplastic cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art

Art Unit: 1636

without undue experimentation (*United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

- 1) Nature of the invention. The invention as it pertains to treatment of certain neoplastic cells, *in vitro* and *in vivo*, is well represented in the art as evidenced by the amount of prior art literature. However, it is not clear from this literature that all types of neoplastic cells are susceptible to the treatments recited by applicant in the claims.
- 2) Scope of the invention. The scope of the invention is very broad and encompasses all types of neoplastic cells. However, it is known by applicant (evidenced by the citation of relevant passages in the disclosure of the instant application and the inclusion of pertinent references in the information disclosure statement) that not all neoplastic cells fall into the categories for which applicant's methods are known to be effective. For example, only about half of all tumors have functionally impaired p53 (see *Medical Oncology* 15: 222-228, 1998), while only about 30% of all tumors have mutations in ras genes (see *Cancer Research* 49: 4682-4689, 1989).
- 3) Unpredictability of the art. The art is unpredictable in terms of what effect these methods of treatment will have, for example, on neoplastic cells not resulting from mutations in the ras or p53 genes. As a result, the skilled artisan would be required to perform undue trial and error experimentation to ascertain if applicant's methods were adequate for the treatment of a particular cellular composition.

Art Unit: 1636

4) State of the art. The state of the art at the time of the invention is unclear on how applicant's methods will affect cellular compositions containing neoplastic cells that do not arise from mutations in the ras or p53 genes.

5) Number of working examples. Applicant only provides working examples using cellular compositions containing neoplastic cells arising from activated ras mutations.

6) Amount of guidance provided by applicant. Applicant provides no guidance as to the effectiveness of the claimed methodology concerning non-ras mutation harboring neoplastic cells

7) Level of skill in the art. Because the mechanism of action for this methodology in neoplastic cells arising from non-ras and non-p53 related events is unknown, the level of skill required in the art is high; however, given the unpredictability of the art and the lack of guidance provided by applicant, the skilled artisan would need to practice trial and error experimentation in order to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in ascertaining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Art Unit: 1636

Claim 1 (and all dependent claims) recites the limitation "collecting the treated cellular composition". It is unclear if there is any additional step required to satisfy this limitation, or if simply treating the cells so as to substantially kill neoplastic cells inherently gives you a collection of treated cells. In the interest of compact prosecution, and because no methodology appears to include specific collection steps, the limitation is being interpreted as set forth above in the latter portion of the statement.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8 and 24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 and 21 of copending Application No. 09/847,356 (Patent Application No. US 2002/0006398 A1). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are genus claims which would be anticipated by the specific claims reciting a reovirus because it is obvious that a reovirus is a virus.

Art Unit: 1636

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 9-11, 13-15 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by McCormick, WO 94/18992.

McCormick describes the use of adenovirus mutants mutated in E1A and E1B so as not to bind to Rb and p53, respectively, whereby said virus selectively causes ablation of neoplastic cells upon contacting a cellular population with the virus (see page 5, line 7 to page 6, line 35).

This anticipates each of the claims as indicated above.

Claims 1, 9-11, 13-15, 20 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by McCormick, US Patent No. 5,801,029.

McCormick describes the use of adenovirus mutants mutated in E1A and E1B so as not to bind to Rb and p53, respectively, whereby said virus selectively causes ablation of neoplastic cells upon contacting a cellular population with the virus (see column 3, line 35 to column 4, line 36). This anticipates each of the claims as indicated above.

Claim Rejections - 35 USC § 103

Art Unit: 1636

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2-6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCormick (both WO 94/18992 and US Patent No. 5,801,029) in view of Lee et al. (US Patent No. 6,136,307).

Applicant's invention is the use of viruses to selectively kill neoplastic cells from a cellular composition outside of a living organism. Limitations of this invention include the

Art Unit: 1636

treatment of hematopoietic stem cells harvested from bone marrow or blood, tissues, organs or cultured cells. The tissues or organs could then be used in transplantation. Additionally, the viruses can be mutated in a gene that inhibits double stranded RNA kinase (PKR). The method may also contain the limitation of adding interferon prior to or simultaneously with the virus, wherein the virus is an interferon sensitive virus such as vesicular stomatitis virus (VSV). Furthermore, the virus can be stored in a solution containing DMSO. The virus can also be removed from the cells after treatment.

McCormick describes a method of using viruses, specifically an adenovirus, to selectively remove neoplastic cells from a cellular population (see page 5, line 7 to page 6, line 35 in WO 94/18992 or column 3, line 35 to column 4, line 36 in US 6,136,307). McCormick does not teach the use of hematopoietic cells, tissue or organs as the cell populations to be treated with viruses.

Lee, et al., teaches the use of hematopoietic neoplasms that can be treated with viruses (see the abstract, etc.). This cellular composition, by its nature, represents a tissue.

McCormick is modified by Lee, et al., to include the treatment of neoplastic hematopoietic cells in the method of selectively killing neoplastic cells. The ordinary skilled artisan would have been motivated to make this modification because hematopoietic stem cells can be contaminated with neoplastic cells, therefore a method of killing those neoplastic cells would be beneficial to the stem cell population. It would have been obvious to make this modification because hematopoietic cells are present in a cellular population, therefore the method of McCormick would also apply to hematopoietic cells. Furthermore, Lee, et al., shows

Art Unit: 1636

that these cells can be selectively killed using viruses in an organism, therefore they could obviously be killed by such a manner outside of an organism.

Given the teachings of the stated prior art and the level of skill of the ordinary skilled artisan at the time of the applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over McCormick (both WO 94/18992 and US Patent No. 5,801,029) in view of Lee et al. (US Patent No. 6,136,307) as applied to claims 2-6 and 8 above, and further in view of Bensinger (Bone Marrow Trans. 21: 113-115).

Applicant's invention is as described above.

McCormick in view of Lee, et al., teaches the use of hematopoietic cells as a cellular composition that can be treated by selectively killing neoplastic cells. McCormick in view of Lee, et al., does not teach the use of these cells for transplantation.

Bensinger is a review article which teaches a technique called purging, where hematopoietic stem cells are selected by a complicated process to remove possible contaminating myeloma cells, so that these cells may be used in a transplantation procedure (see entire document).

McCormick in view of Lee, et al., is modified by Bensinger by further using the treated hematopoietic cells as transplants. The ordinary skilled artisan would have been motivated to combine these teachings because the purging technique described by Bensinger is inefficient and complicated in achieving a goal that the methods of McCormick in view of Lee, et al., more

Art Unit: 1636

efficiently achieve. It would have been obvious to combine these teachings because the end result of both methods is the preparation of a cellular population that is substantially free of neoplastic cells.

Given the teachings of the stated prior art and the level of skill of the ordinary skilled artisan at the time of the applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over McCormick (both WO 94/18992 and US Patent No. 5,801,029) in view of Strong, et al., (EMBO J. 17(12): 3351-3362 (1998)).

Applicant's invention is as described above.

McCormick describes a method of using viruses, specifically an adenovirus, to selectively remove neoplastic cells from a cellular population (see page 5, line 7 to page 6, line 35 in WO 94/18992 or column 3, line 35 to column 4, line 36 in US 6,136,307). McCormick does not teach further mutating the virus to contain mutations that prevent the inhibition of PKR.

Strong, et al., teaches that PKR is inhibitory to the nature of viral infection, and that neoplastic cells which have activated ras pathways can overcome the inhibitory nature of PKR to viral infection.

McCormick is modified by Strong, et al., to additionally contain mutations in the PKR inhibitory genes. The ordinary skilled artisan would have been motivated to combine these teachings so that the virus will only affect cells that are neoplastic as a result of activated ras pathways while being ineffectual towards non-neoplastic cells, thus increasing the selectivity of

Art Unit: 1636

the viral treatment. It would have been obvious to combine these teachings because the end result, the selective infection and oncolysis of neoplastic cells, is the same in both teachings.

Given the teachings of the stated prior art and the level of skill of the ordinary skilled artisan at the time of the applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCormick (both WO 94/18992 and US Patent No. 5,801,029) in view of Stojdl, et al. (Nature Medicine 6(7): 821-825 (2000)).

Applicant's invention is the same as described above.

McCormick describes a method of using a virus to selectively remove neoplastic cells from a cellular population (see page 5, line 7 to page 6, line 35 in WO 94/18992 or column 3, line 35 to column 4, line 36 in US 6,136,307). McCormick does not teach the use of interferon treatment to enhance the effectiveness of the treatment, nor does it teach the use of VSV specifically.

Stojdl, et al., teaches that cancer cells, while being non-responsive to interferon treatment, have acquired a compromised nature in terms of viral infection, and that treatment of these cells with VSV in the presence of interferon resulted in oncolysis while normal cells remained relatively unaffected due to the protection by interferon (see abstract).

McCormick is modified by Stojdl, et al., to combine the use of interferon treatment in the exposure of cellular populations to viral treatment for the selective killing of neoplastic cells. In addition, McCormick is modified to make use of the VSV virus in the treatment of neoplastic

Art Unit: 1636

cells. The ordinary skilled artisan would have been motivated to combine these teachings to increase the effectiveness of the selective killing of neoplastic cells by viruses, as well as to increase the range of viruses that are useful in said treatment. It would have been obvious to combine the teachings because the end result of both methods, the selective killing of neoplastic cells, is the same.

Given the teachings of the stated prior art and the level of skill of the ordinary skilled artisan at the time of the applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCormick (both WO 94/18992 and US Patent No. 5,801,029) in view of Stewart, et al. (Bone Marrow Trans. 23: 111-117 (1999)).

Applicant's invention is the same as described above.

McCormick describes a method of using viruses, specifically an adenovirus, to selectively remove neoplastic cells from a cellular population (see page 5, line 7 to page 6, line 35 in WO 94/18992 or column 3, line 35 to column 4, line 36 in US 6,136,307). McCormick does not teach the storage of the resulting cells in a solution of DMSO.

Stewart, et al., teaches the storage of blood stem cells in a solution of DMSO (see page 112 right column, last paragraph).

McCormick is modified by Stewart, et al., to include the storage of the treated hematopoietic cells in a solution containing DMSO. The ordinary skilled artisan would have been motivated to combine these teachings in order to increase the amount of time the treated

Art Unit: 1636

cells were viable for, rather than to have to produce fresh cells every time they were needed. It would have been obvious to combine these methods because the method of storing cells described by Stewart, et al., is a common storage method.

Given the teachings of the stated prior art and the level of skill of the ordinary skilled artisan at the time of the applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Allowable Subject Matter

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A Lambertson whose telephone number is (703) 308-8365.

The examiner can normally be reached on 8am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
August 23, 2002

DAVID GUZO
PRIMARY EXAMINER
David Guzo